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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/153,133	09/15/1998	D. DUKE LEE	04712/018002	5068

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CLARK & ELBING LLP
101 FEDERAL STREET
BOSTON, MA 02110

EXAMINER	
SHARAREH, SHAHNAM J	

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 05/04/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/153,133	LEE ET AL.	
	Examiner	Art Unit	
	Shahnam Sharareh	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *45,46,49-54,56-61 and 64-72* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *45,46,49-54,56-61 and 64-72* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on February 17, 2006 has been entered.

Amendment filed on February 17, 2006 has been entered. Claims 45-46, 49-54, 56-61, 64-72 are pending. Any rejection that is not addressed in this Office Action is considered obviated in view of the claim amendments.

Priority

1. Priority of the instant application as set forth in Paper No. 6 is September 15, 1998.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

2. Claims 45-46, 58-61, 72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Reyveld US Patent 4,016,252 in view of Poser US Patent 5,968,253.

The instant claims are directed to vaccine formulations comprising a calcium phosphate and an immunogen wherein the formulation is a hardenable, injectable paste having a solid content of greater than or equal to 40%wt.

Relyveld teaches the state of art for using calcium phosphate to improve the efficacy of vaccine formulations. Reyvald teaches injectable gel calcium phosphate vaccine formulations comprising an immunogens from various bacteria and viruses (see abstract, col 2, lines 1-5, col 3-4). The calcium to phosphate ratio in gel formulation of Relyveld is from 1.62 to 1.85 (abstract, col 2 lines 1-15, col 3-4). Reyveld also teaches the use of other conventional adjuvants such as aluminum hydroxide or phosphate. (see

col 2, lines 6-10). Therefore, Reyveld teaches the appropriate range of calcium and phosphate concentrations in the final formulation. Reyvald lacks in teachings a paste formulation having about 40% solid content.

Poser discloses extended release paste-like flowable injectable compositions comprising 60-95% tricalcium phosphate, a second calcium phosphate source such as monocalcium phosphate monohydrate in a powder form, in combination with an antibiotic and an aqueous injectable lubricant (see abstract, col 6, lines 48-67; col 13, lines 19-51). Poser's tricalcium phosphate meets the limitation of the instant calcium phosphate. The tricalcium phosphate of Poser is present in dry amount above the 40% by weight of the composition. Such amounts meet solid content of the instantly claimed composition. Poser formulates a depot delivery system to provide extended release exposure of the agent of choice into the system (see col 7, lines 1-20). Poser's monocalcium phosphate monohydrate meets the limitation of the instant adjuvant. Poser meets all functional limitations of the instantly claimed composition.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time of invention to modify the physical characteristics of Relyveld's formulation according to the teachings of Poser and change the gel formulation of Reyveld's vaccine to a paste-like formulation by routine experimentations to optimize the described calcium phosphate concentrations. One of ordinary skill in the art would have been motivated to modify Relyveld's gel formulation into paste to formulate a depot extended release.

3. Claims 49-54, 56-57, 64-72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Reyveld US Patent 4,016,252 in view of Poser US Patent 5,968,253 as applied to claims 45-46, 58-61, 72 and further in view of Classen.

The combined teachings of Reyveld and Poser are described above. Reyveld allows for the use of suitable adjuvants such as aluminum hydroxide or calcium phosphates (col 2, lines 6-10). Reyveld and Poser however do not teach the explicit use of an additional adjuvant and/or cytokine in their combination.

Classen is used to provide general knowledge in the art of vaccine formulations. Classen teaches the use of various cytokines in combination with an immunogenic agent to enhance the clinical response. (col 17, lines 6-67). Classen specifically states that a group of immune modulators, namely cytokines, are "immunocyte receptor ligands" that are capable of binding to cell receptors of immune mediator cells in a non-antigen specific manner to cause the induction of immune response. (col 17, lines 5-16). Specifically, Classen states that they use of cytokines in a vaccine formulation improves its efficacy because cytokines modulate target cells by interacting with cytokine receptors on the target cells (see col 17, lines 48-55).

Classen also describes the use of such carrier systems that include depot adjuvants such as aluminum hydroxide and calcium phosphate salts to prolong the release of immunogenic agent. (see col 20, lines 40-50). Classen teaches vaccines for inducing an immunologic response in humans comprising an immunogen and a depot adjuvant (abstract, col 15-17, col 53, lines 10-55; col 54, lines 40-46). Classen also provides for various modes of injectable compositions for use in intramuscular or

subcutaneous administration. (col 20, lines 56-60; col 52, lines 25-50). Classen does not explicitly describe the specific combination of an immunogen with a calcium phosphate, a cytokine and a secondary adjuvant.

Even though Reyveld and Poser fails to explicitly use cytokine or an additional adjuvant in their combined formulation, it would have been obvious to one of ordinary skill in the art at the time of invention to employ a cytokine or immunogenic adjuvant, as described by Classen, because addition of either or both cytokines and secondary adjuvants would have increased the specificity, the duration of exposure and further improved the induction of an immune response.

One of ordinary skill in the art would have had a reasonable expectation of success to further modify the Reyveld and Poser combination by adding a cytokine or a secondary adjuvants because incorporation of such agents to improve the clinical effects of vaccine is well described in the art.

Claims 45-46, 58-61, 72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Reyveld US Patent 4,016,252 In view of Gerhart et al US Patent 5,085,861 and Constantz et al US Patent 5,782,971.

The teachings of Reyveld are described above. Reyveld fails to explicitly teach a hardenable past with a solid content of about 40% wt.

Gerhard disclose calcium phosphate containing compositions comprising biocompatible calcium phosphate ceramics that can be in the form of an injectable or moldable paste and will solidify within 10 minutes after administration. (see abstract; col 7, lines 30-46, 60-67; col 8, lines 1-20; examples 2-3). The particle size of Gerhard's

compositions falls within the instantly claimed nanocrystalline (see col 7, lines 15-25). Gerhard's compositions contain active agents that are readily used in treatment of cancers such as bone tumor (col 13, lines 45-67).

Constantz et al teach amorphous calcium phosphate containing compositions that are used as suitable drug delivery vehicles (col 2, lines 60-67; col 6, lines 61-63). Constantz specifically teaches paste formulations of calcium phosphate that are capable of hardening after administration at the site of interest (col 6, lines 40-64). Constantz's composition comprise about 15 wt% of the dry ingredient (solid component) having particle sizes of about 0.5- 500 microns (col 5 lines 1-3; and lines 14-25). Constantz further indicates that one of ordinary skill in the art would be able to modify the viscosity of his composition by varying the percentages of solids in his composition, thus allowing for ease of administration (col 6, lines 32-39). Constantz suggests the use of an additional calcium phosphate and also states that the calcium to phosphate ratio of such compositions should be about 1.6 to about 1.8 (see col 3, lines 5-20; col 5, lines 1-10, claims 1-5). Constantz finally suggests preparing kits to ease access and preparation (see col 7, lines 1-10). Constantz lacks the specific teaching of an anticancer agent in combination with the calcium phosphate vehicle.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time of invention to modify physical characteristics of Reyveld's composition into an injectable paste, as suggested by Gerhard and Constantz, and formulate a hardenable calcium phosphate formulation that is easily administered to a site of interest, because the ordinary artisan would have had a reasonable expectation of success in achieving

the same clinical result. Finally, absent a showing of unexpected results, to achieve optimal clinical effects, the ordinary artisan would have had a reasonable expectation of success to optimize the solid content concentrations of such formulation by routine experimentation.

Response to Arguments

The Declaration filed on February 17, 2006 under 37 CFR §§ 1.131 and 1.132 has been considered but is ineffective to overcome the Poser reference US Patent 5,968,253.

The evidence submitted is insufficient to establish applicant's alleged actual reduction to practice of the invention in this country or a NAFTA or WTO member country after the effective date of the Poser reference.

As the initial matter, Examiner failed to locate Appendix A, copies of PCT/US97/18528, as refereed in the Declaration. Second, Applicant has not provided any evidence as to what part of the PCT/US97/18528 was exactly reduced to practice to antedate the teachings of Poser et al in US Patent 5,968,253.

Third, Applicant's declaration appears to constructively claim the benefit of prior-filed PCT application under 35 U.S.C. 120, 121, or 365(c). However, Applicant is informed that copendency between the current application and the prior application is required. Since the applications or any of its US counterparts were not copending, any claim to the prior-filed nonprovisional application is improper. Applicant is required to delete the reference to the prior-filed application from the first sentence(s) of the specification, or the application data sheet, depending on where the reference was

originally submitted, unless applicant can establish copendency between the applications. Accordingly, the rejections of record are maintained for the reasons set forth above.

Conclusion

No claims are allowed. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shahnam Sharareh whose telephone number is 571-272-0630. The examiner can normally be reached on 8:30 am - 6:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan, PhD can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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SREENI PADMANABHAN
SUPERVISORY PATENT EXAMINER